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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,713	11/27/2000	Dale B. Schenk	15270J-004741US	9870

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,713	SCHENK, DALE B.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,56-59,61 and 63-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,56-59,61 and 63-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/1/05 has been entered. As requested, applicant's after-final amendment and response filed on 11/2/04 has been entered and considered, including the exhibit, Bard et al. Claims 33, 56-59, 61, and 63-152 are pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Applicant's supplemental IDS submitted on 2/1/05 has been considered and an initialed signed copy of the 1449 is attached to this office action.

Claim Rejections - 35 USC 112

Claims 33, 56-59, 61 and 63-152 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention as claimed, is maintained in part. Applicant's arguments have been fully considered, including the Bard et al. reference, but have not been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

As noted in the advisory action mailed to applicant's on 12/20/04, applicant's arguments are largely a reiteration of their previous arguments made in the response filed on 3/23/04 based on evidence made of record in the response filed on 6/23/03. These arguments have been addressed in full in the office actions mailed on 10/24/03 and 6/3/04 and were not found persuasive in overcoming the instant grounds of rejection for reasons of record. New arguments regarding the specific teachings of Verma et al. and the teachings of the post-filing reference, Bard et al., are discussed below.

Regarding applicant's new argument based on the newly submitted evidence of Bard et al., it is noted that Bard et al. was published more than 5 years after the effective filing date of the instant application. The applicant is reminded that as stated in *In re Glass*, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. The Bard et al. reference provides data concerning the ability of various monoclonal murine antibodies to bind to capture soluble Aβ, bind to Aβ present in plaque, and reduce neuritic dystrophy. Please note that Bard et al. is not analogous to the instant invention as Bard et al. teaches the direct administration of monoclonal antibody, not DNA encoding the heavy and light chains of the antibody. It is further

noted that of the antibodies discussed in Bard, only the 10D5 antibody is disclosed by the applicant. The remaining antibodies are not disclosed in the specification, nor are they chimeric, humanized, or human as required by the claims. Furthermore, in contrast to the applicant's argument that Bard et al. provides direct evidence that antibodies other than 10D5 are effective in binding Aβ *in vivo* and thus could be used in the instant invention as claimed, Bard et al. demonstrates that the treatment of disease characterized by amyloid plaques using monoclonal antibodies is unpredictable and affected by not only the isotype of the antibody, but by the affinity of the antibodies for Fc receptors on microglial cells rather than the affinity of the antibody for Aβ. Of the monoclonal antibodies tested by Bard et al., including the IgG1 antibody 10D5, Bard et al. shows that only two antibodies, both IgG2a isotype antibodies which recognized the 3-7 epitope of Aβ, were capable of providing neuronal protection and having any significant effect on neuritic dystrophy, following direct *in vivo* administration of the antibodies (see Bard et al., page 2027, Figure 4, particularly b and c, and column 2 paragraph 3). In fact, the 10D5 antibody disclosed in the specification did not reduce neuritic pathology (Bard et al., see the legend to Figure 4, page 2027). Thus, the Bard et al. reference in fact strengthens the position of the office as to the unpredictability of treating or preventing a disease characterized by amyloid plaques comprising Aβ peptide using any antibody which binds to an epitope within Aβ1-10. Further, in regards to the two IgG2a antibodies which were actually shown to have some effect after passive administration, it is noted that the specification fails to disclose these antibodies, or further fails to provide any guidance as to the effects of antibody isotype on treatment efficacy. Also, as noted above, Bard et al. does not provide any evidence that overcomes the art recognized unpredictability of administering DNA encoding a heavy and light

chain antibody for treating or preventing a disease characterized by amyloid plaques comprising Aβ peptide of record. Therefore, applicant's arguments regarding Bard et al. are not found persuasive.

In regards to the teachings of Verma et al., the applicant now argues that because Verma et al. states that, " to correct blood-clotting disorders, such as hemophilia, all that is needed is a therapeutic level of clotting protein in the plasma", citing Verma et al. on page 239, column 1, paragraph 3, that this means that Verma et al. considered the treatment of disease by transiently expressing a protein in blood to be predictable. In fact, Verma et al. comes to no such conclusion. Despite the clear goal of expressing a therapeutic level of a protein such as a clotting protein in the plasma at a certain level, Verma et al. concludes that this goal has not been reached using the currently available vectors due to problems with gene delivery and expression. These problems have been discussed in detail in the previous office actions. As stated in the previous action, Verma et al. still concludes that as of 1997 the practice of therapeutic gene expression for treating disease is plagued by problems including problems specific to different vector types, and general problems with levels of gene expression and exposure of the gene product to the target tissue. The previous office action also cited other evidence, Marshall et al., Orkin et al., and Eck et al. Marshall et al. discusses advances in therapeutic gene transfer; however, based on all the evidence, Marshall summarizes the prospects for predictable gene therapy of disease as , "many problems must be solved before gene therapy will be useful for more than the **rare** application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1, emphasis added). Orkin et al. was also cited in the previous office action and again while discussing some rare successes and advances in gene transfer technology, clearly states, "

.. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4, and page 8, paragraph 2). Eck et al. concurs with the conclusions of Verma, Marshall, and Orkin. Eck et al. reports that despite numerous clinical trials in progress, gene therapy is still in its infancy. While all the cited references agree that therapeutic gene transfer has potential and that advances in gene transfer technology will likely occur, at the time of filing, the state of the art of therapeutic gene transfer to treat disease was unpredictable. Therefore, applicant's arguments regarding Verma et al. do not overcome the evidence of record for the unpredictability of therapeutic gene expression *in vivo* to treat disease.

Further, as stated in previous office actions, based on the level of unpredictability in the art at the time of filing, the onus is on the specification to provide the missing disclosure for achieving successful treatment or prophylaxis of diseases characterized by amyloid plaques comprising Aβ peptide using DNA encoding antibodies which bind to an epitope in Aβ1–10 . However, as discussed in detail in the previous office actions, the specification fails to provide the requisite teachings to enable the practice of the scope of the invention as claimed. The specification is primarily directed to immunization with Aβ peptides or with the passive transfer of monoclonal protein antibodies. The specifications teachings regarding the delivery of DNA encoding an antibody which binds to an epitope within Aβ1-10 are limited to a brief and general

description of gene transfer and vectors on page 25 of the specification and are entirely prophetic. The specification provides no specific guidance as to particular vectors which are in fact capable of expressing sufficient levels of any encoded antibody over multiple administrations resulting in treatment of diseases such as Alzheimer's disease. Based on the combined teachings of Marshall et al., Eck et al., Verma et al., and Orkin et al., it is clear that more is required to predict success since all the vector systems listed on page 25 suffer from limitations that undermine their therapeutic usefulness. Furthermore, the specification provides no guidance as to any nucleic acid sequences encoding any antibody which binds to an epitope within Aβ1-10 or within Aβ1-5 whose expression in the blood or any other location in the body at any level or duration or expression would be sufficient to reduce or prevent amyloid plaques or plaque formation. The closest evidence provided by the specification concerns the passive administration of protein antibodies. However, this evidence of record demonstrates further complicates the issue since the evidence demonstrates that even with direct administration of protein antibody which binds to an epitope within Aβ1-10, therapeutic efficacy is not predictable. Example XI shows that administration of the 2H3 antibody directed against an epitope within Aβ1-12 was ineffective in preventing or ameliorating plaque deposits in transgenic mice due to problems with rapid antibody clearance. Further, as discussed in detail above, the Bard et al. reference provided by the applicants clearly demonstrates that unpredictability of actually treating neuritic pathology when administering monoclonal antibodies which actually bind to Aβ peptide in plaques and even have some efficacy in reducing Aβ peptide concentrations *in vivo*. Thus, the evidence or record shows that even following direct protein antibody administration, the treatment of disease associated with amyloid plaques with

antibodies that bind to an epitope within Aβ1-10 is not predictable. Therefore, based on the art-recognized unpredictability of achieving therapeutic levels of gene expression using currently available vectors at the time of filing, the unpredictability in treating or preventing diseases associated with amyloid plaques comprising Aβ peptide using any monoclonal antibody that binds to an epitope within Aβ1-10 as evidenced by the specification, the limitation of the applicant's working examples to the administration of protein antibody and not nucleic acid encoding an antibody, the lack of specific guidance as to vectors, promoters, routes of vector administration, or nucleic acid sequences encoding antibodies which are capable of treating or preventing diseases associated with amyloid plaque formation, or specifically Alzheimer's disease, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER